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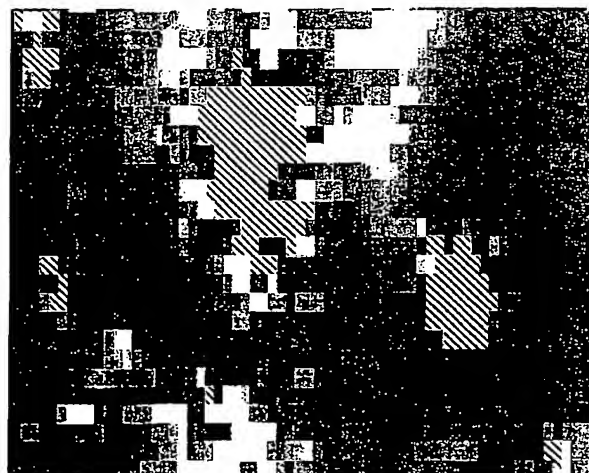
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[Continued on next page]

(54) Title: THREE-DIMENSIONAL TISSUE HARDNESS IMAGING



(57) Abstract: A method for generating hardness information of tissue subject to a varying pressure. The method comprises receiving signals from the tissue with a sensor for measuring the deformation of the tissue in a measuring plane defined by the sensor, which sensor, during a varying pressure exerted on the tissue, is moved along the tissue in a direction transverse to the measuring plane; identifying strain of the tissue from the resulting signals; and relating the strain to elasticity and/or hardness parameters of the tissue. The method may comprise the step of displaying elasticity and/or hardness parameters of a tissue surface or tissue volume part extending practically parallel to the direction of motion of the sensor.

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## THREE-DIMENSIONAL TISSUE HARDNESS IMAGING

This invention relates to a method for generating hardness information of tissue subject to a varying pressure. In particular, the method relates to a method for generating hardness information of the wall of a blood vessel or body cavity.

5        Such a method is known from European application EP-A 0 908 137. In this application, the strain (deformation) of vessel walls is derived with ultrasound from the relative displacement of a more inward layer and a more outward layer of the vessel wall as a result of the pressure varying through the heartbeat. These relative displacements are (at an assumed  
10        equal speed of sound in the medium) equal to the difference of relative time delays of the ultrasound beam, measured at two times.

      The relative time delay can be measured by correlating with each other sound signals obtained consecutively over time from one specific direction and deriving the relevant time delay from a correlation optimum.  
15        At this optimum, therefore, two signals consecutive over time are maximally correlated when the time difference between the respective signals is equal to the relevant time delay. By taking the difference of time delays measured at two different times and relating this to the time difference between the measuring times, it is possible to derive the degree of strain of the vessel  
20        wall in the direction of the sound beam as a result of pressure changes induced by the heartbeat.

      By measuring the local relative displacements with a measuring beam in a specific direction and performing this measurement in a measuring plane oriented transversely to the vessel wall, it is possible to  
25        display elasticity information about respective measuring positions in the measuring plane. Furthermore, by measuring an average relative

displacement along the above directions, a so-called palpogram can be composed, which is indicative of the hardness of the vessel wall in the plane in which the vessel wall cuts the measuring plane. The information derivable from such an elastogram/palpogram is important to identify and characterize plaques on the vessel walls. The composition of plaques can be important to the assessment of their injuriousness to health.

Such information is often not derivable from a conventional echogram, since the image of high-risk cannot be distinguished from less high-risk plaques.

Moreover, practical and theoretical studies show that the degree of strain of the vessel wall is indicative of the stresses that can occur in such plaques. If the stresses become too high, a plaque can tear open, so that a life-threatening thrombosis can arise.

Although for a two-dimensional cross-section satisfactory measuring results can be obtained, in practice there appears to be a need for a three-dimensional display of the hardness information of the wall, so that the elasticity/hardness of at least one surface part of the vessel wall can be measured. With the present technique, it is practically very difficult to reproducibly analyze a blood vessel in such a manner. Furthermore, on the basis of conventional echographic data it is very hard to localize a suspect spot in a blood vessel. In fact, the performance of a single transverse scan at selected positions in a blood vessel provides insufficient information to enable determination of the presence or absence of plaques in the blood vessel as a whole.

The invention has for its object to meet such need and to provide a method with which 3D information about the elasticity and/or hardness of a wall of a body cavity, in particular a blood vessel, can be obtained in a consistent and reproducible manner. In this connection, it is observed that with the present conventional technique the correlation between consecutive images is optimized by positioning the sensor as stably as possible, because

movement of the sensor in general has a negative effect on the correlation. The invention is based on the insight that precisely by performing a motion transverse to the measuring plane a sufficient correlation between consecutive images can be maintained to enable detection of hardness  
5 and/or elasticity properties.

Accordingly, this object is achieved if the method of the above-mentioned type comprises the following steps of:

- receiving signals from the tissue with a sensor for measuring the deformation of the tissue in a measuring plane defined by the sensor, which  
10 sensor, during a varying pressure exerted on the tissue, is moved along the tissue in a direction transverse to the measuring plane;
- identifying strain of the tissue from the resulting signals; and
- relating the strain to elasticity and/or hardness parameters of the tissue.

15 According to the invention, signals are received from *e.g.* a vessel wall in a preferably almost continuous motion, consecutive (groups of) frames still having a sufficient correlation to enable distillation of the relevant information. This can be determined by means of a probability function indicating the relation between consecutive images. By controlling the  
20 motion (or feeding back feedback position) related to this probability function, an optimum palpogram quality is obtained, which can even be more favorable than in a stationary arrangement.

The method preferably comprises the step of displaying elasticity and/or hardness parameters of the tissue surface or tissue volume part  
25 extending practically parallel to the direction of motion of the sensor, if required combined with position information of the sensor and/or the tissue. The deformation can be determined with an acoustic or optical sensor detecting echographic or optical data.

In a further preferred embodiment, signals possessing an optimum overlap are received. An optimum overlap can be determined by means of a probability function displaying the similarity between consecutive signals.

In the alternative or in addition thereto, at an assumed cyclic  
5 pressure change, signals can be received at predetermined time intervals in the period of the motion. In a preferred embodiment, these are signals of a blood vessel wall, the data being received only during a specific time interval of the period of the heartbeat. An advantage thereof is that signals that are not or less suitable for the determination of elasticity and/or  
10 hardness information of the tissue need not be stored, as a result of which data storage capacity can be performed to a limited extent, and the data processing can be significantly simplified.

The invention has a special use in case the tissue is an artery moving through the heartbeat in the longitudinal direction. In that case, the sensor  
15 can be moved practically parallel to this direction, so that during at least one detection period the sensor a practically fixed position relative to the tissue. Practice shows that in particular in or near the heart, where relatively strong longitudinal motions of the artery occur, a strongly improved recording of hardness and/or elasticity properties, compared to the  
20 conventional recording technique, is obtained in a measuring plane transverse to the vessel wall.

The invention further relates to an apparatus for using a method according to the invention, comprising:

- a sensor movable through a blood vessel or body cavity for recording  
25 signals from the tissue;
- a processor device for collecting and processing signals from the sensor to identify strain of the tissue and to relate the strain to elasticity and/or hardness parameters of a tissue surface or tissue volume part extending practically parallel to the direction of motion of the sensor; and

a display device for displaying elasticity and/or hardness parameters of the tissue surface or tissue volume part.

In a preferred embodiment, the apparatus further comprises a position recording means coupled with the processor device to record sensor positions. The position recording means can display the 3D coordinates of the sensor relative to a fixed reference, *e.g.* by means of (electromagnetic) bearings, or in a simpler embodiment it may be a relative linear measure from *e.g.* the point where a catheter is inserted or from a specific fixed location in a blood vessel.

In a mechanized use, the apparatus may be provided with an actuator for moving the sensor. Preferably, the actuator has an adjustable speed of motion. Position recording may thereby occur by means of measuring and/or adjusting the speed of motion of the sensor and/or the actuator.

In a further preferred embodiment, activating means are provided to activate data storage means for recording signals. Further activating means may be provided to activate the actuator. The activating means may be connected with an ECG recording device. In this manner, signals can be received from a blood vessel, the data being received only during a specific time interval of the period of the heartbeat. In the alternative or in addition thereto, the activating means may detect the correlation between consecutive echographic images and activate the data storage means at a the predetermined correlation.

In another further preferred embodiment, the sensor is arranged in a catheter, which can be inserted into a blood vessel, which sensor can record signals under controlled pullback of the catheter.

The invention will further be explained on the basis of the description of the drawings, in which:

Fig. 1 is a diagrammatic representation of the apparatus according to the invention;

Fig. 2a is a 3D palpogram of a phantom with a soft plaque part;

Fig. 2b is a longitudinal section of the 3D palpogram of Fig. 2a, combined with conventional echographic information;

Fig. 3 is a series of six 3D palpograms of a similar aorta part of a rabbit, obtained in six different measurements; and

Fig. 4 is a 3D palpogram of a human coronary artery, obtained *in vivo*.

Fig. 1 is a diagrammatic representation of the apparatus 1 according to the invention. This apparatus comprises a movable catheter 2 provided with an acoustic sensor 3. A processor 4 is present to collect and process echographic data; the processor 4 is connected with a display device 5. The processor 4 is further in contact with a position recording means 6 for recording the position of the sensor 3.

The catheter 2 can be moved through a blood vessel 7, which blood vessel 7 has a vessel wall 8 deformed by the heartbeat. The deformation can be derived by the processor 4 from the echographic data of the catheter 2 and related to elasticity and/or hardness parameters of the wall 8.

In explanation, a plaque 9 is shown in the blood vessel 7. This plaque comprises a fat core 10 closed by a harder cap 11. The motion of the catheter 2 is controlled by an actuator 12. The actuator 12 has an adjustable speed of motion, such that the catheter can be moved at a speed of 0.1-2 mm/s. The preferred direction is a so-called pullback direction, *i.e.* the catheter 2 is inserted until a maximum insertion depth and is then pulled back by the actuator 12. The actuator can pull the catheter 2 back in a practically continuous motion. The actuator 12 can be activated by the activating means 13.

In the alternative, the activating means 13 can be controlled by data from an ECG device 14, so that a favorable moment of the heartbeat can be selected to perform a measurement. This will be explained below in more



detail. During the performance of the measurement, the motion can be interrupted, so that an intermittent pullback motion can be performed. The activating means 13 can also be coupled with a data storage means 15 for storing echographic data. This ensures that the extensive amount of  
5 echographic data is received only during a relevant part of the heartbeat, which results in a favorable capacity saving and significantly simplifies the data processing.

Besides through selection of a relevant part of the heartbeat for the performance of the palpographic measurement, the activating means can be  
10 connected, additionally or alternatively, with correlation-detection means 16 detecting the correlation between consecutive echographic images to become active at a predetermined correlation.

The method according to the invention will be explained below. At a varying pressure as a result of the heartbeat, echographic data are received  
15 by the acoustic sensor 3, while the sensor 3 is moved along the vessel wall 8. The echographic data can be analyzed by a processor 4, strain of the vessel wall 8 being identified from the resulting echographic data; and the strain being related to elasticity and/or hardness parameters of the vessel wall 8. In this manner, it is possible to display elasticity and/or hardness  
20 parameters of a tissue surface or tissue volume part extending practically parallel to the direction of motion of the sensor. In a preferred embodiment, in such a display, i.e. a palpogram or an elastogram of the vessel wall, the position information of the sensor and/or the tissue is displayed as well. The motion can be a practically continuous motion; in the alternative, an  
25 intermittent motion can be performed. The motion and/or the analysis of echographic data can be controlled, so that the echographic data are received at predetermined time intervals in the period of the heartbeat, at which time interval the motion may be interrupted.

In the alternative, only those signals possessing an overlap can be received. An optimum overlap can be determined by means of a probability function displaying the similarity between consecutive signals.

5 The palpogram of Fig. 2a has been obtained by scanning a phantom with a soft inclusion, shown in cross-section by the echogram of Fig. 2b. The phantom has the shape of a hollow tube and is made of polyvinyl alcohol cryogel. The inclusion comprises a harder cap, which may also be present in a naturally formed plaque. The thickness of the cap varies from 2 mm to 800  $\mu\text{m}$ .

10 The inclusion thus has mechanical properties corresponding to those of a plaque that may be present in a natural blood vessel.

The phantom was kept under water and subjected to a pulsatile pressure. A catheter provided with an acoustic converter was moved through the phantom at a speed of 1.0 mm/s. The number of acquired 15 frames was about 30 per second, *i.e.* an axial displacement of 0.03 mm per image. At a beam width of about 0.6 mm, this proved to be an acceptable amount.

In the soft part, a strain until 1% was observed. The strain increases with a decreasing thickness of the cap.

20 The palpograms of Fig. 3 have been obtained by scanning an arteriosclerotic aorta of a New Zealand White rabbit at a pullback speed of 0.5 and 1 mm/s., respectively. In this Figure, a) is a first scan; b) is a second scan obtained after the catheter was positioned again; and c) is a scan obtained some time after, with the catheter again being inserted into the 25 animal.

The palpograms have been obtained at a speed of motion of the catheter of 1.0 mm/s. In the palpograms, the plaque is always clearly visible as a lighter region.

In all cases, the following measuring method was used:

30 1. contour detection;

2. selection of frames with a minimum mutual motion;
3. estimating the displacement of the wall between two frames;
4. deriving the strain;
5. averaging the strain per angle;
- 5 6. (color) coding the strain at the contour.

Of three patients a palpogram was obtained; Fig. 4 shows an example thereof. The hatched regions do not represent available measuring values, as a result of the presence of a side branch of the aorta. As appears from the Figure, the largest strain occurs in the regions around the side branch (light  
10 regions). It turned out that the motion of the catheter was slight enough to determine a reliable palpogram during a heartbeat. The degree of overlap between consecutive frames always remained at least about 70%.

In an experiment, a palpogram was obtained in which the data were divided into heart cycles, using the R-wave of the ECG signal. Because of  
15 the natural motion of the catheter through the varying speed of flow of the blood and the contraction of the heart, the catheter moves deeper into the coronary artery during the diastolic phase. Therefore, measurement is performed during this phase (*i.e.* a decreasing pressure of the heart and an increasing speed of flow), and the catheter is pulled out against the natural  
20 motion. This was done at a speed between 0.5 and 1.0 mm/s, by means of a mechanical actuator (Trakback, JoMed Imaging, Rancho Cordova, CA, USA).

It turned out that through this motion the sensor, during the detection period, has a practically fixed position relative to the wall of the  
25 artery. It was found that the motion from the measuring plane is minimized, so that the quality of the palpogram is improved.

Although the invention has been discussed on the basis of the above-mentioned exemplary embodiment, in which the presence of plaques in a blood vessel was checked, it is clear that the invention can also be used  
30 when detecting and analyzing other tissues, such as (for cancer research of)

the prostate, the esophagus etc. Instead of measuring deformations as a result of a naturally varying pressure, the apparatus can be provided with means for artificially exerting a pressure variation on the tissue.

Furthermore, all kinds of variations and modifications may be used  
5 without departing from the spirit of the invention. Such variations may *e.g.* comprise the display of a 3D palpogram as a stack of 2D palpograms; the display of the angle at which measurement is performed; or a combination display of a palpogram and an angiogram.

Such and other variations are deemed to be within reach and the  
10 scope of protection of the appended claims.

## CLAIMS

1. A method for generating hardness information of tissue subject to a varying pressure; comprising the steps of:
  - receiving signals from the tissue with a sensor for measuring the deformation of the tissue in a measuring plane defined by the sensor, which  
5 sensor, during a varying pressure exerted on the tissue, is moved along the tissue in a direction transverse to the measuring plane;
  - identifying strain of the tissue from the resulting signals; and
  - relating the strain to elasticity and/or hardness parameters of the tissue.
- 10 2. A method according to claim 1, characterized in that the method comprises the steps of
  - correlating signals consecutive over time, which signals are representative of the deformation of the tissue in case of positions of the  
15 sensor mutually moved with respect to each other; and
  - calculating by means of this correlation strain in a tissue surface or tissue volume part extending practically parallel to the direction of motion of the sensor.
- 20 3. A method according to claim 1 or 2, characterized in that the method comprises the step of displaying elasticity and/or hardness parameters of a tissue surface or tissue volume part.
4. A method according to at least one of the preceding claims,  
25 characterized in that the signals are echographic data detected with an acoustic sensor.

5. A method according to at least one of the preceding claims, characterized in that the signals are optical data detected with an optical sensor.
- 5 6. A method according to at least one of the preceding claims, characterized in that the method comprises the step of displaying elasticity and/or hardness parameters of the tissue with position information of the sensor and/or the tissue.
- 10 7. A method according to at least one of the preceding claims, characterized in that the signals are received during a practically continuous motion of the sensor.
8. A method according to at least one of the preceding claims,  
15 characterized in that signals possessing an overlap are received.
9. A method according to claim 8, characterized in that an optimum overlap is determined by means of a probability function displaying the similarity between consecutive signals.
- 20 10. A method according to at least one of the preceding claims, characterized in that signals, at an assumed cyclic pressure change, are received at predetermined time intervals in the period of the motion.
- 25 11. A method according to at least one of the preceding claims, characterized in that the signals come from a blood vessel wall and that the data are received only during a specific time interval of the period of the heartbeat.

12. A method according to at least one of the preceding claims, characterized in that the tissue is an artery moving through the heartbeat in the longitudinal direction, and that the sensor is moved practically parallel to this direction, so that, during at least one detection period, the  
5 sensor has a practically fixed position relative to the wall of the artery.

13. An apparatus for using the method according to at least one of the preceding claims, characterized in that the apparatus comprises:

- a sensor movable through a blood vessel or body cavity for recording  
10 signals from the tissue;
- a processor device for collecting and processing signals from the sensor to identify strain of the tissue and to relate the strain to elasticity and/or hardness parameters of a tissue surface or tissue volume part; and
- a display device for displaying elasticity and/or hardness parameters  
15 of the tissue surface or tissue volume part.

14. An apparatus according to claim 13, characterized in that apparatus comprises correlation detection means detecting the correlation between consecutive signals, which signals are representative of the deformation of  
20 the tissue in case of positions of the sensor mutually moved with respect to each other; the processor device being arranged to calculate by means of this correlation a strain in a tissue surface or tissue volume part extending practically parallel to the direction of motion of the sensor.

25 15. An apparatus according to claim 13 or 14, characterized in that the apparatus further comprises:

- a position recording means coupled with the processor device to record sensor positions.

16. An apparatus according to claims 13-15, characterized in that the apparatus further comprises:

- an actuator for moving the sensor.

5 17. An apparatus according to claim 16, characterized in that the actuator has an adjustable speed of motion.

18. An apparatus according to at least one of claims 13-17, characterized in that the apparatus further comprises:

- 10 - first activating means for activating data storage means for storing signals.

19. An apparatus according to at least one of the preceding claims 13-18, characterized in that the apparatus comprises:

- 15 - second activating means for activating the actuator.

20. An apparatus according to at least one of claims 18 or 19, characterized in that the activating means can be connected with an ECG recording device to become active during a predetermined part of the  
20 heartbeat.

21. An apparatus according to at least one of claims 18-20, characterized in that the activating means are connected with the correlation detection means to become active at a predetermined correlation.

25

22. An apparatus according to at least one of claims 13-21, characterized in that the sensor is arranged in a catheter, which can be inserted into a blood vessel, the sensor recording signals under controlled pullback of the catheter.

30



23. An apparatus according to at least one of claims 13-22, characterized in that the sensor is an acoustic sensor.

24. An apparatus according to at least one of claims 13-22, characterized  
5 in that the sensor is an optical sensor.

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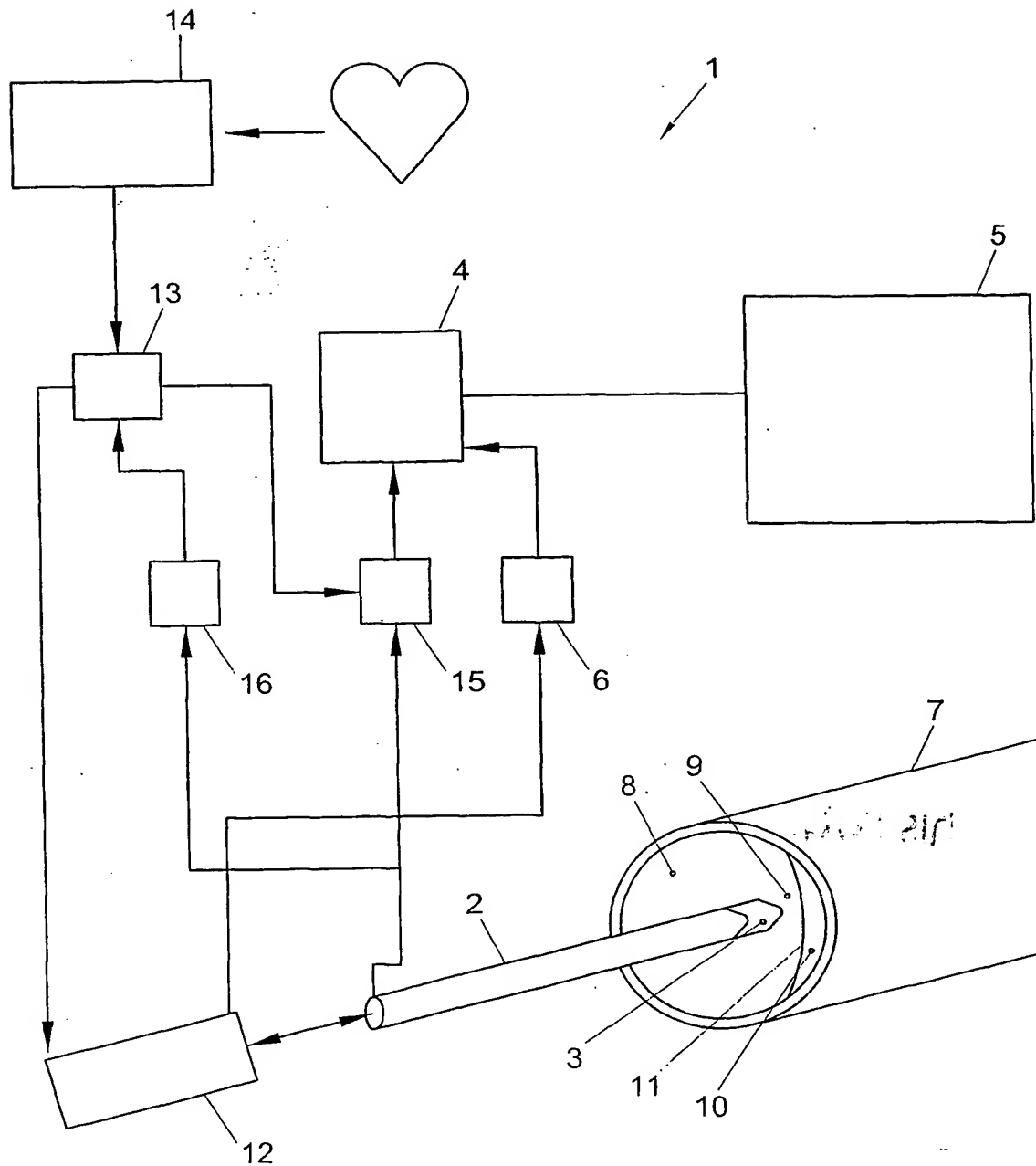


Fig. 1

- |                       |                           |
|-----------------------|---------------------------|
| 1. Apparatus          | 9. Plaque                 |
| 2. Catheter           | 10. Fat core              |
| 3. Sensor             | 11. Harder cap            |
| 4. Processor          | 12. Actuator              |
| 5. Display device     | 13. Activating            |
| 6. Position recording | 14. ECG device            |
| 7. Blood vessel       | 15. Data storage          |
| 8. Vessel wall        | 16. Correlation detection |

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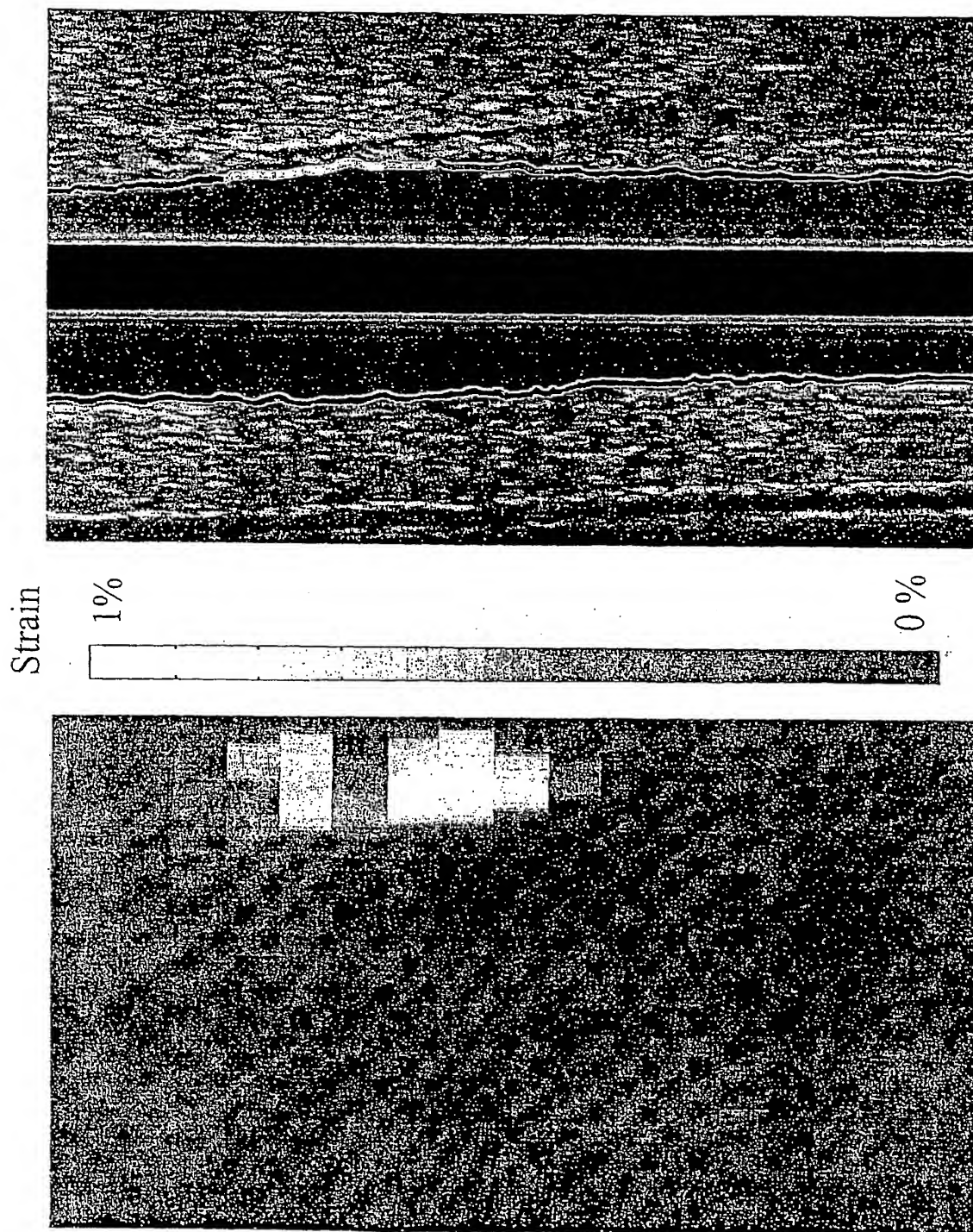


Fig. 2b

Fig. 2a

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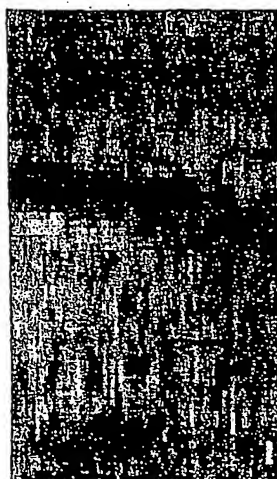


Fig. 3c

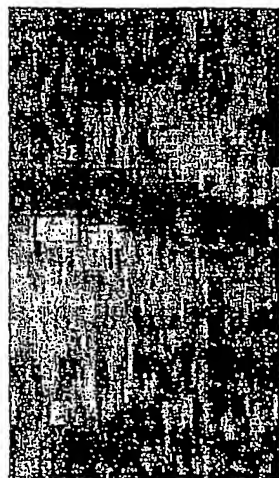
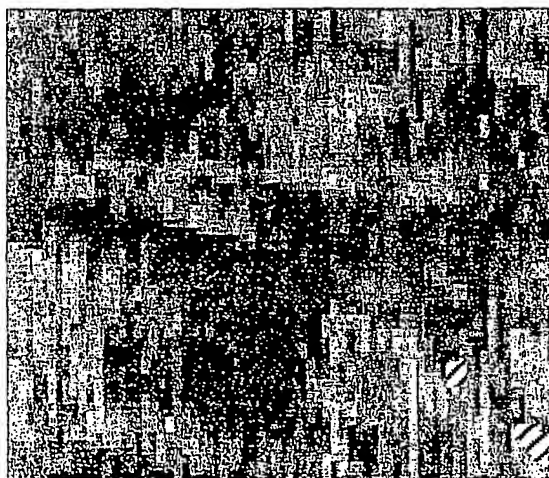


Fig. 3b

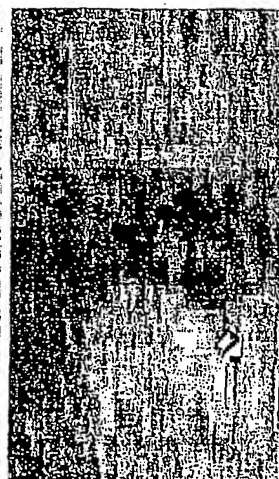


Fig. 3a

1mm/s

0,5mm/s

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Fig. 4

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## INTERNATIONAL SEARCH REPORT

PCT/NL 02/00572

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61B8/12

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 848 969 A (MCGEE DAVID ET AL) 15 December 1998 (1998-12-15)	13, 15-20, 22-24
Y	column 6, line 61 - line 65 column 7, line 32 - line 54 column 9, line 35 - line 40 column 10, line 51 - column 11, line 25 column 12, line 57 - line 67 column 19, line 56 - line 60	14
X	US 6 099 471 A (KRISTOFFERSON KJELL ET AL) 8 August 2000 (2000-08-08)	13,18,23
Y	column 5, line 1 - line 5 column 8, line 53 - column 9, line 8 figure 1	14

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

21 November 2002

Date of mailing of the international search report

29/11/2002

Name and mailing address of the ISA

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Authorized officer

Martelli, L

# INTERNATIONAL SEARCH REPORT

PCT/NL 02/00572

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-12  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/NL 02/00572

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5848969	A	15-12-1998	NONE	
US 6099471	A	08-08-2000	BR 9814063 A	26-09-2000
			BR 9814067 A	26-09-2000
			CA 2305724 A1	15-04-1999
			CA 2305725 A1	15-04-1999
			CN 1301207 T	27-06-2001
			CN 1281538 T	24-01-2001
			EP 1024922 A1	09-08-2000
			EP 1021657 A1	26-07-2000
			WO 9917905 A1	15-04-1999
			WO 9918358 A1	15-04-1999
			US 6463655 B1	15-10-2002
			US 6253792 B1	03-07-2001

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